

REMARKS

Claims 47-48 are pending in the application. Applicants request entry and consideration of the amendments and response herein. Accordingly, claims 47 and 49-100 will be pending in the application upon entry of this amendment.

Applicants wish to thank the Examiner for the courtesy extended to their undersigned representative in the interview on December 14, 2004. Further to that discussion, Applicants submit these amendments and response.

Amendment of any claim herein is not to be construed as acquiescence to any of the rejections/objections set forth in the instant Office Action, and was done solely to expedite prosecution of the application. Applicants make these amendments without prejudice to pursuing the original subject matter of this application in a later filed application claiming benefit of the instant application, including without prejudice to any determination of equivalents of the claimed subject matter. Support for these amendments appears throughout the specification and claims as filed. No new matter is introduced by these amendments.

Claim Amendments

Applicants have amended claim 47. This amendment is made to more clearly delineate the claimed subject matter and correct text errors. No new matter is introduced by this amendment.

Claims 49-54 have been added and are directed towards the treatment of various diseases defined in claim 48. Claims 55-100 have been added and are directed towards pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier. No new matter is introduced by this amendment.

Claims Rejections – 35 U.S.C. §112, First Paragraph

It is alleged that claims 47-48 do not reasonably provide enablement for all disorders generically embraced in claim 47. It is further alleged that the scope of the claims includes not

only any or all conditions but also those conditions yet to be discovered as mediated by interleukin-12 overproduction, for which it is alleged there is no enabling disclosure. In addition, it is alleged that the Applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language. Applicants disagree and respectfully traverse.

IL-12 overproduction is known to cause excessive Th1 response, and may result in inflammatory disorders, such as rheumatoid arthritis, Crohn's disease, multiple sclerosis, sepsis, and psoriasis. It is therefore indicated that compounds that down-regulate IL-12 production can be used for treating inflammatory diseases.

The Examiner concludes that the specification enables the invention for the treatment of rheumatoid arthritis. Administration of pyrimidine compound 12 reproducibly reduced the arthritic score and delayed development of polyarthritis in a dose-dependent manner in the Adjuvant arthritis model (see Example 29 in the Specification at page 28, line 30). The Examiner has therefore acknowledged that a method of treatment of rheumatoid arthritis is enabled by the instant invention.

The enablement requirement for the treatment of Crohn's disease in claim 39 was not acknowledged by the Examiner. A method of treatment of Crohn's disease in rats was determined by treatment with the pyrimidine compounds of the instant invention. In a Crohn's disease rat model, it was found that compound 12 of the instant invention reduced colonic inflammation, and that the reduced inflammation could be attenuated with different doses (see Example 29 of the Specification at page 31, line 13). In view of these results, Applicants submit that the enablement requirement to treat Crohn's disease has been satisfied. Further, the reduction in colonic inflammation clearly demonstrates the potential of the pyrimidine compounds of the instant invention in the treatment of inflammatory bowel disease.

In addition, it is known to those of ordinary skill in the art that using compounds to lower Th1 cytokine levels to treat Crohn's disease has enjoyed initial success.¹ Th1 cytokines, such as TNF- α and IL-12, are thought to have a primary role in initiating Crohn's disease, as well as in ongoing inflammatory reactions. The use of anti-TNF- α (antibody) therapy, to reduce the levels of TNF- α , has been utilized in patients with Crohn's disease.¹ A significant clinical response

¹ (a) Cominelli, F. New England Journal of Medicine (2004), 351, p. 2045. (b) Mannon, P. J. et al. New England Journal of Medicine (2004), 351, p. 2069.

has been observed. Further, the use of anti-IL-12 has been used in an NIH study in the treatment of patients with Crohn's disease.¹ It was found that anti-IL-12 induces clinical responses and remissions of Crohn's disease, and that the treatment was associated with decreases in Th1-mediated inflammatory cytokines.

Because TNF- α and IL-12 are both Th1 cytokines, and treating Crohn's disease using antibodies has enjoyed initial success, one of ordinary skill in the art would appreciate that lowering IL-12 production with pyrimidine compounds of the instant invention could provide similar results. Applicants therefore submit that they satisfy the enablement requirement of 35 U.S.C. §112 for treating Crohn's disease.

The treatment of multiple sclerosis (MS) using antibody treatment is also known to those of ordinary skill in the art.² It is also known that in patients with MS, IL-12 secretion is markedly increased. One method of treating MS involves antibody treatment with anti-IL-12, presumably to lower IL-12 levels. In animal models, it has been demonstrated that treating Experimental Autoimmune Encephalomyelitis, EAE (animal model of MS), with anti-IL-12 significantly reduced the EAE severity and incidence and severity of EAE relapse. Further, administration of IL-12 to the animal models with EAE increased the severity of EAE. It is therefore indicated that methods which lower IL-12 levels, by antibody treatment or treatment with other compounds/compositions, are useful for treating MS. Based on the foregoing and the fact that Applicants have demonstrated that compounds in the instant application lower IL-12 levels, Applicants submit that the enablement requirement of 35 U.S.C. §112 for treating MS is satisfied.

The potential treatment of diabetes mellitus using antibody treatment is also known to those of ordinary skill in the art.^{2,3} It is known that administration of IL-12 induces the rapid onset of insulin-dependent diabetes mellitus in the NOD (non-obese diabetic) mouse. One method of treating diabetes mellitus would involve antibody treatment with anti-IL-12, presumably to lower IL-12 levels. Administration of anti-IL-12 is known to help suppress islet destruction.⁴ By suppressing islet destruction, anti-IL-12 is indicated to treat diseases which result from islet destruction, including diabetes mellitus. Based on the foregoing and the fact

² (a) Balashov, K. E. et al. Proc. Natl. Acad. Sci. USA. (1997), 94, p. 599. (b) Constantinescu, C. S. Journal of Immunology. (1998), p. 5097.

³ Trembleau, S. et al. J. Exp. Med. (1995), 181, p. 817.

⁴ Ma, L. et al. Diabetes. (2003), 52, p. 1976.

that Applicants have demonstrated that compounds in the instant application lower IL-12 levels, Applicants submit that the enablement requirement of 35 U.S.C. §112 for treating diabetes mellitus is satisfied.

The treatment of psoriasis using antibody treatment is also known to those of ordinary skill in the art.⁵ It is also known that significant amounts of IL-12 are observed in rats with psoriasis. One method of psoriasis treatment involved antibody treatment with anti-IL-12, presumably to lower IL-12 levels. In a psoriatic model that closely resembles human pathology, mice were first subjected to IL-12, and then treated with anti-IL-12. In these mice, psoriasis (or the lesions associated with psoriasis) did not develop, but in the control group (mice treated with an agent that induces psoriasis-like lesions), over 90% of the mice developed psoriasis.⁴ It is therefore indicated that methods which lower IL-12 levels, by antibody treatment or treatment with other compounds/compositions, are useful for treating psoriasis. Based on the foregoing and the fact that Applicants have demonstrated that compounds in the instant application lower IL-12 levels, Applicants submit that the enablement requirement of 35 U.S.C. §112 for treating psoriasis is satisfied.

The treatment of septic shock (resulting from sepsis) using antibody treatment is also known to those of ordinary skill in the art.⁶ It is also known that septic shock results from the release of IFN- γ which is induced by IL-12, which can be induced by LPS (lipopolysaccharide). One method of septic shock treatment involved antibody treatment with anti-IL-12, presumably to lower IL-12 levels. In *in vivo* mouse studies, mice were first subjected to LPS, and then treated with anti-IL-12. In these mice, septic shock, measured by observing IFN- γ levels, was five to sixfold lower than controls (LPS treated mice).⁵ It is therefore indicated that methods which lower IL-12 levels, by antibody treatment or treatment with other compounds/compositions, are useful for treating septic shock. Based on the foregoing and the fact that Applicants have demonstrated that compounds in the instant application lower IL-12 levels, Applicants submit that the enablement requirement of 35 U.S.C. §112 for treating sepsis is satisfied.

Thus, methods of lowering IL-12 levels have been indicated to be viable in treating a number of IL-12 overproduction related disorders, such as rheumatoid arthritis, Crohn's disease,

⁵ Hong, K. et al. *Journal of Immunology*. (1999), p. 7480.

⁶ Mattner, F. et al. *Infection and Immunity*. (1997), p. 4737.

MS, diabetes mellitus, psoriasis, and sepsis. Applicants therefore submit that the use of their instant triazine compounds, in view of the knowledge of the results observed using the above-mentioned treatments to lower TNF- α and IL-12 levels, satisfy the enablement requirement of 35 U.S.C. §112 for treating IL-12 overproduction related disorders. Applicants respectfully request withdrawal of this rejection.


CONCLUSION

In view of the above, reconsideration and withdrawal of all rejections and allowance of the application with claims 47 and 49-100 are respectfully solicited. Accordingly, the Examiner is respectfully requested to pass this application to issue. Should any of the claims not be found to be allowable, the Examiner is requested to telephone Applicants' undersigned representative at the number below. Applicants thank the Examiner in advance for this courtesy.

The Director is hereby authorized to charge or credit any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 04-1105, under Order No. 50586-61254 CON.

Respectfully submitted,

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